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OSWALD THEODORE AVERY

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OSWALD THEODORE AVERY was born in Halifax, Nova Scotia, on October 21, 1877. He came to the United States with his family at an early age, settling in New York City, where he spent all of his active scientific life. He was a man of great simplicity and singleness of purpose, endowed with unusual powers of concentration on those matters of science which aroused his curiosity; and the interest they evoked endured throughout his life. He was by nature somewhat reticent and seldom permitted the ordinary distractions of life to divert him from those scientific problems in which he was so completely immersed. The long list of his achievements which grew in importance to the very end of his life is testimony of his capacity for logical and progressive thinking and for using and developing for his purposes his own techniques and those of other sciences, particularly those of biochemistry.

Avery was graduated with an A. B. degree from Colgate University in 1900, and received his M. D. degree from the College of Physicians and Surgeons of Columbia University in 1904. After graduation from medical school, Avery spent a few years in the practice of clinical medicine, which supplied him with some amusing stories but did not attract him sufficiently for him to make his career in that field. He subsequently joined and cooperated with Benjamin White, Director of the Hoagland Laboratory in Brooklyn, where he became Associate Director of the Division of Bacteriology. Thus he instinctively selected the subject to which he was to devote his life

work and in which he was later to become famous. While here he began to familiarize himself with the activities of certain species of bacteria and their relationship to infectious diseases. The work from the very beginning led him in the direction of analytical thinking and of the investigation of the subject of immunity. The character of his work attracted the interest of Dr. Rufus Cole, Director of the Hospital of the Rockefeller Institute, who invited him to become a member of that organization, with which he became associated in 1913. Here he found satisfaction and happiness and the environment which he needed for the full development of his growing interest in bacteriology. He continued as a member of the staff of the Rockefeller Hospital until his retirement in 1948 and, during this time, among other bacteriological and immunological subjects, he devoted himself in large part to the study of a single microorganism, the pneumococcus, the cause of lobar pneumonia, until more was known about that organism than about almost any other bacterium. The volume of Avery's work was large and its breadth was such that its implications for bacteriology in general and related fields were of profound significance.

During the time when Avery was progressively developing his knowledge of the pneumococcus, he promoted and engaged in, with the assistance of his colleagues, a number of important investigations of general bacteriological interest, using the pneumococcus and certain other microorganisms for this purpose. With K. G. Dernby he determined the optimum and limiting hydrogen ion concentration for the growth of the pneumococcus and showed that the observed concentrations for the growth of bacterial races are probably as definite and characteristic as those for enzyme action. With G. E. Cullen he showed that the final hydrogen ion concentration reached in the growth of a hemolytic streptococcus differed between strains of human and bovine origin as to the ultimate end point. This demonstration constituted a simple and rapid method for the differentiation of human and bovine types of streptococcus hemolyticus. It is of some interest that in the studies of the different types of pneumococcus all the fermentable carbohydrates used gave identical results in the rate of reaction change and in the final hydrogen ion concentration reached.

Avery participated with Theodor Thjotta and H. J. Morgan in a number of studies on bacterial nutrition. It had been shown that the microorganism hemophilus influenzae, a strictly hemoglobinophilic organism, will grow in hemoglobin free medium consisting of plain broth enriched by sterile suspensions or extracts of mucoid bacteria. This observation was extended by a study of the growth requirements of the so-called hemophilic bacilli of which H. influenzae served as a type. The growth stimulating action of extracts of yeast and of vegetable cells, and the importance of blood as a source of growth accessory substances were studied. The growth of H. influenzae depends upon two distinct and separable substances. Both are present in blood, but neither alone suffices for growth. One is a vitamin-like substance extractable from red blood cells, yeast, and vegetable cells, and is relatively heat labile; and the other is an iron-containing substance which is heat stable and is present in red blood cells. Both occur in plant as well as in animal tissue, so that sterile raw potato serves as a substitude for blood in the cultivation of H. influenza. Further studies showed that plant tissue also has a growth accelerating action on other microorganisms such as pneumococcus, streptococcus hemolyticus, and streptococcus viridans. It also facilitates the growth of anaerobic bacteria under aerobic conditions, since it furnishes certain necessary growth accessory substances and provides an oxidizing-reducing system whose action destroys toxic peroxides of bacterial origin.

In a series of studies in cooperation with J. M. Neill, Avery presented the results of an examination of the nature of the oxidation-reduction systems of sterile extracts of pneumococcus. These active systems consist of two components: (1) a thermo-labile constituent of the pneumococcus cell which is not removed by washing; (2) thermo-stable substances which are lacking in washed cells and which are not necessarily of pneumococcus origin, since they may be

supplied by muscle infusion and yeast extract. The character of these reactions is determined by the presence or absence of molecular oxygen. In the presence of molecular oxygen, active extracts were shown to exhibit the following activities: consumption of molecular oxygen, formation of peroxide, oxidation of hemoglobin, and oxidation and destruction of the hemolysin and intracellular enzymes contained in pneumococcus extracts. All of these oxidations are examples of "oxygen activation," whereby substances themselves not reactive with molecular oxygen are easily oxidized by agents formed during the oxidation of other substances. Analysis of these processes shows that the active systems consist of two components, one of which is thermo-labile, the other thermo-stable. By themselves the thermo-stable substances react slowly with molecular oxygen to form oxidizing agents, and in the absence of molecular oxygen they establish conditions under which methemoglobin and other substances are slowly reduced. In the presence of the thermo-labile component, the reactions of oxidation and reduction are markedly accelerated. This latter component is wholly nonreactive with molecular oxygen, possesses no reducing power, and seems to be catalytic in nature. When present together, these substances constitute systems responsible for many of the biological oxidations and reductions of the living cell.

Avery in collaboration with G. E. Cullen made an interesting study of the intracellular enzymes of pneumococcus and, as a result, suggested their relationship to the metabolic activity of the cell. The demonstration of the intracellular agents was affected by breaking down the cell structure by suitable means and making extracts which were tested for enzymatic activity. In this way, active cell-free agents were obtained which hydrolyzed intact protein to some extent and which hydrolyzed peptones with striking avidity. An active esterase was also isolated as were such carbohydrate-splitting enzymes as invertase, amylase, and inulinase. On the other hand, fermentation of dextrose could not be demonstrated. These studies indicated that the enzymes described were not secretory products of the pneumococcus

but were of the nature of endo-enzymes, since their activity could be demonstrated only when cell disintegration had occurred.

At the time when Avery joined the staff of the Hospital of the Rockefeller Institute, the study of the pneumococcus and its relationship to lobar pneumonia had been in progress for about three years. As a result of this study, pneumococci had been separated by means of immunological reactions into two different groups by Dochez and Gillespie. The first group consisted of Types I, II, and III, which could be sharply differentiated from one another by serological tests and were found only in association with severe examples of lobar pneumonia or in the mouths of individuals in close contact with such cases of pneumonia. The other group consisted of strains associated with lobar pneumonia in a much smaller percentage of instances, and was of greater serological diversity. These latter strains resembled the varying types of pneumococcus found in the mouths of healthy normal individuals. On his arrival, Avery joined in the study of the immunological classification of pneumococci and added to this classification several new serological types. As the study passed to other hands, many new immunological types were discovered. On the whole, the original Types I, II, and III remained fairly constant in from 60 to 80 percent of cases as the causative agents of the severe and highly fatal instances of lobar pneumonia. The results of these studies brought about a more exact knowledge of the character of pneumococcus infection of the lung, and shed a considerable amount of new light on the etiology and epidemiology of lobar pneumonia.

In 1917 Dochez and Avery reported the elaboration of a specific soluble substance by the pneumococcus during its growth in culture medium. This substance was identical immunologically with the type of pneumococcus growing in the culture and was present in large amounts at a time when little or no cell disintegration had taken place. The substance consequently did not represent dead dissolved bacterial protein, but was due to the elaboration and passage into solution of a substance which was the product of the life activity of the pneumococcus cell. That it was not an intracellular substance

liberated at the death and disintegration of the pneumococcus was proven by the fact that it was already present in considerable quantities at a time when no intracellular hemolysin was present in the culture medium. The intracellular hemolysin is liberated only on the death and disintegration of the cell, and the curve of hemolysin did not begin to rise until a time when the curve of the soluble substance had almost attained its maximum elevation.

The formation of a soluble substance by the pneumococcus on growth in vitro suggested the probability that an analogous substance would be formed on growth of the organism in the animal body, and because of the readiness with which the substance passed into solution it was expected that there would be no difficulty in demonstrating it in the body fluids of animals experimentally infected with pneumococcus and in those of human beings suffering from lobar pneumonia. This was found to be the case, since a specific precipitin reaction with antipneumococcus serum corresponding to the type of organism with which the animal or human being was infected was easily demonstrated in the blood serum and urine during the period of infection. The discovery of this substance was of great importance to Avery's subsequent study of the pneumococcus, since it served as the point of departure for much of his succeeding research.

From 1922 onward, Avery, Heidelberger, and their associates undertook a chemical study of the soluble specific substances, which Avery believed were an important key to the whole subject of the immunological specificity of bacteria. Papers were published showing that the soluble specific substances of the pneumococcus were polysaccharides, the first instance in which carbohydrates were shown to be involved in immune reactions. The soluble substances of Type II and Type III pneumococci were found to be nitrogen-free carbohydrates, the former made up mainly of glucose, and the latter composed of aldobionic acid units. The Type I polysaccharide was nitrogen-containing, and made up in part of galactouronic acid.

Differences in bacterial specificity were related by Avery and Heidelberger to characteristic chemical differences in the substances responsible; where these substances were similar, cross-reactivities were found to occur, and accounted chemically for the observed specificities. A whole new field of bacteriology, immunology, and chemistry was opened up. Many puzzling and confused observations in bacteriology and immunology were thus clarified and systematized on a rational chemical basis. At least a part of the virulence, specificity, and behavior of many important bacteria is referable to a specific polysaccharide and in the encapsulated microorganism this is the major factor. Here, then, is one of the principal foundation stones of the science of immunochemistry, which is rapidly including an ever-widening study of artificial and natural antigens.

Meanwhile, in the hands of Avery and his co-workers, knowledge of the specific characters of the pneumococci and the manner in which these are acquired had been moving to a new pinnacle of achievement. The culmination of this knowledge and of the studies conducted by Avery and his co-workers, Dawson, Alloway, MacLeod, McCarty, Taylor, and Hotchkiss, came with the announcement, in 1944, that the fundamental constituent of the transforming agent of pneumococcus Type III is a polymerized desoxyribonucleic acid. That the transformation of one type of pneumococcus into a pneumococcus of another type could occur in vivo was first demonstrated by Griffith in 1928. Studies on the mechanism of experimental transformation of pneumococcal types were carried out in Avery's laboratory from 1928 to 1948.

The transforming substance was extracted from heat-killed pneumococci or from living cells caused to undergo lysis. Sodium citrate, which inhibits the inactivating effect of pneumococcal desoxyribonuclease, was used in the lysing process in the later procedures. After deproteinization, the desoxyribonucleic acid was further purified, so that an exceedingly minute quantity, 0.0015 microgram per milliliter, was capable in vitro of inducing transformation of susceptible cells under proper cultural conditions. Evidence that the transforming agent is a nucleic acid of the desoxyribose type was obtained by

chemical, enzymatic, serologic, and physico-chemical studies of highly purified material. Elementary analysis showed that the material closely resembles authentic preparations of desoxyribonucleic acid of animal origin. Serological procedures with anti-pneumococcal sera of appropriate type failed to reveal the presence of capsular or somatic polysaccharides or of pneumococcus protein in the transforming material, each of which would easily have been demonstrated by such tests.

Amino acids were obtained on hydrolysis in so small an amount that not more than 0.2 percent of protein could be present. Later studies showed that glycine from the degradation of adenine was apparently the only amino acid present in the hydrolysate, so that the possibility that a specific protein or nucleoprotein, rather than the nucleic acid itself, was responsible for the transforming activity seemed to have been excluded decisively.

Highly purified preparations of the transforming agent obtained from pneumococcus Type III made possible for the first time the induction of a predictable and permanent alteration in a heritable character of the living cell by means of a chemically defined substance of known nature. In other words, a specific mutation was induced as a result of specific treatment, an achievement which had long eluded biologists. The broad implications of the discovery of the nature of the transforming agent became apparent when it was demonstrated in Avery's laboratory that desoxyribonucleic acids, separated from a number of other types of pneumococci, possess predictable transforming activity relative to a specific cell character. Confirmatory evidence supporting Avery's interpretation of the transformation phenomenon was later obtained in other laboratories with both pneumococcus and other microorganisms.

As a result of these studies of Avery and his associates, it became apparent that certain polymerized desoxyribonucleic acids are concerned with the heredity of microbial cells in much the same fashion that genes are concerned with the hereditary characteristics of higher organisms.

The impact of these findings upon prevailing concepts of investigators in cytology, genetics, and virology, already aware that desoxyribonucleic acid is a prominent constituent of nuclei, chromosomes, and viruses, was of great importance. It was now learned that this constituent is the one functionally operative in transmitting the manifold biologic capacities and potentialities of the germ plasm. This, in turn, indicated to biochemists that nucleic acids are capable of innumerable variations in composition and structure. Both of these concepts have received considerable support, and it has become increasingly evident that they play an important part in the orienting of investigations in the several fields concerned with cellular development and differentiation.

At the time the above investigation was being presented, from its beginning to its successful conclusion in 1948, Avery and certain of his associates engaged in a number of collateral studies related to the immunological significance of carbohydrates, both those of bacterial origin and certain more common sugars. As a result of these studies an antigenic relationship was shown to exist between the polysaccharides and pneumococcus and those of certain types of Bacillus Friedlander and of a number of plant gums, such as gum acacia. Following this, a study of the specificity of certain azo-protein antigens containing simple saccharides of known chemical constitution was undertaken with W. F. Goebel. This study showed unequivocally that the specificity of carbohydrates was determined by their chemical constitution and that differences in structure, no matter how slight, were invariably reflected in the specificity of the antibodies which such antigens evoked. As an example, the specific polysaccharide of Pneumococcus Type T is characterized by the presence of a highly labile acetyl group. Gentle removal of this group deprives this polysaccharide of its antigenicity in certain animals and alters its over-all serological specificity as well.

A species-specific carbohydrate distinct from the capsular polysaccharide was isolated from the somatic component of pneumococci. This substance was designated as Fraction C. It subsequently became

of considerable interest, since it gave rise to a precipitating antibody in the serum of patients suffering from pneumonia, which was present only during the acute phase of the disease and disappeared during convalescence. The antibody is not specific for pneumonia, but also occurs during the acute phase of a number of infections, such as rheumatic fever, and in conditions associated with tissue degeneration. Its presence or absence is now regularly used as a measure of the activity of the clinical condition under study.

During this time Avery in collaboration with René Dubos investigated the action of a bacterial enzyme which decomposed the polysaccharide of Pneumococcus Type III, both in vitro and in vivo. This enzyme, when injected in conjunction with virulent Type III pneumococcus, was capable of protecting mice, rabbits, and monkeys against experimental infection because of its capacity of stripping the virulent cell of its protective capsular coat. This constituted one of the very early demonstrations of antibiotic action against pathogenic microorganisms, a procedure which has since become of great importance in the cure of numerous infectious diseases.

Avery also participated with Dochez and Lancefield in an immunological classification and antigenic analysis of the hemolytic streptococcus. This study proved that this organism is not a unit type, as was previously supposed, but consists of a number of types which can be definitely identified serologically. Subsequent development and employment of the techniques used resulted in the establishment of the hemolytic streptococcus as the causative agent of scarlet fever, acute rheumatic fever, and hemorrhagic nephritis, all of which diseases may now be brought within the range of prevention or cure by antibiotic agents effective against the hemolytic streptococcus.

Avery, by his studies of the chemical basis for the differences between the several types of pneumococcus and the importance of carbohydrates in determining the antigenic specificity of bacterial and synthetic antigens, became one of the founders of the modern science of immunochemistry, a science which has rapidly come to include an ever-widening range of studies of artificial and natural antigens.

During both the First and the Second World Wars, Avery placed his scientific knowledge and skill at the disposal of the United States Government, serving on various committees concerned with the control of a number of important infectious diseases which are prevalent among troops under conditions of warfare. During his active career he received a number of honorary degrees: Sc.D., Colgate University, 1921; L.L.D., McGill University, 1935: Sc.D., New York University, 1947; and Sc.D., Rutgers University 1953. In addition, he was awarded a number of other honors and prizes, among them the Paul Ehrlich Gold Medal and the Copley Medal of the Royal Society of London. He was elected to the National Academy of Sciences in 1933 and was also a foreign member of the Royal Society of London.

Dr. Avery was a true scientist with an insatiable curiosity and a powerful and unremitting urge to discover the innermost mechanisms of the biological facts that came under his observation. His approach to the solution of a problem was characterized by a logical simplicity of thought and a perfection of technical procedure, combined with a complete objectivity that guaranteed the soundness of his deductions. Most of Avery's associations were with his colleagues, by whom he was greatly revered and who have preserved for him a timeless affection. He was a truly lovable person, humble, disinterested, and generous. The inspiring and friendly quality of his leadership is conspicuously represented by his many former associates who now occupy distinguished positions in medicine in the United States and elsewhere, so that his light still burns in many places of learning and research.

KEY TO ABBREVIATIONS

Ann. Int. Med.=Annals of Internal Medicine
Arch. Int. Med.=Archives of Internal Medicine
Arch. Pediat.=Archives of Pediatrics
Centr. Bakt.=Zentralblat für Bakteriologie
J.A.M.A.=Journal of the American Medical Association
J. Exp. Med.=Journal of Experimental Medicine
J. Infect. Dis.=Journal of Infectious Diseases
J. Med. Res.=Journal of Medical Research
Proc. Soc. Exp. Biol. Med.=Proceedings of the Society for Experimental Biology and Medicine
Trans. Assn. Am. Phys.=Transactions of the Association of American Physicians

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